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Enantio- and Diastereocontrolled Synthesis of an Angular Triquinane Sesquiterpene (+)-Arnicenone

Yosuke Iura, Tsutomu Sugahara, and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

konol@mail.cc.tohoku.ac.jp

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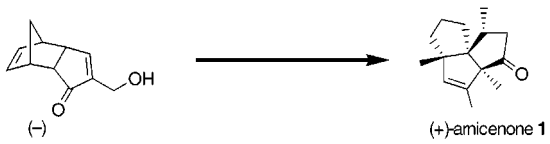
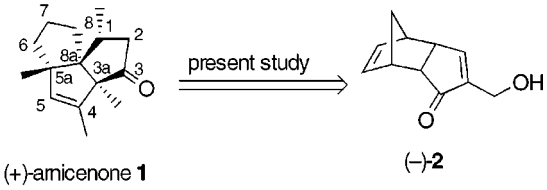
ABSTRACT



(+)-Arnicenone, a sesquiterpene of an angular triquinane isolated from *Arnica* plants, has been synthesized for the first time in an enantiocontrolled manner from a synthetic equivalent of chiral 2-hydroxymethylcyclopentadienone to determine the absolute configuration of the natural product as 1*R*,3a*R*,5a*S*,8a*R*.

We have recently developed an efficient route to the α-hydroxymethylketone **2** serving as a synthetic equivalent of chiral 2-hydroxymethylcyclopentadienone by employing either an enzymatic[1] or a catalytic[2] procedure. Utilizing this chiral building block, which exhibits inherent convex-face selectivity, we attempted diastereoselective construction of (+)-arnicenone[3] **1**, an isocomene-type angular triquinane sesquiterpene isolated from the essential oil of rhizomes and roots of *Arnica* plants, to determine the absolute configuration[4] of this natural product unambiguously as well as to develop a general enantio- and diastereocontrolled route to the isocomene-type sesquiterpenes. We report here the first diastereocontrolled synthesis of (+)-arnicenone **1** from (−)-**2** which allowed determination of the absolute configuration of the natural product unambiguously as 1*R*,3a*R*,5a*S*,8a*R* (Scheme 1).

Scheme 1



Reduction of (−)-**2** with diisobutylaluminum hydride (DIBAL) gave regio- and diastereoselectively the *endo*-allyl alcohol **3**, $[\alpha]^{30}_{D}$ +82.4 (*c* 0.2, $CHCl_3$), as the single product by convex-face selective 1,2-reduction. Treatment of **3** with *N*-bromosuccinimide (NBS)[5] allowed simultaneous discrimination and specific protection of each of the two olefins and two hydroxy functionalities in the molecule to give rise to the single bromo-ether **4**. The Eschenmoser rearrangement reaction[6] was next carried out on the basis of the remaining primary allylic hydroxy and olefin functionalities to furnish

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(2) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *Chem. Commun.* **1998**, 1755. Iura, Y.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1999**, *40*, 5735. Kanada, R. M.; Taniguchi T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 3631. Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *Synlett* **2000**, 1019.
(3) Schmitz, R.; Frahm, A. W.; Kating, H. *Phytochemistry* **1980**, *19*, 1477.
(4) According to Fitjer's conclusion in the determination of the absolute configuration of natural (−)-α-isocomene **1** (=O = =H_2), natural (+)-arnicenone **1** should have the same absolute configuration as the latter afforded the former on Wolff−Kishner reduction,[3] see: Fitjer, L.; Monzo-Oltra, H. *J. Org. Chem.* **1993**, *58*, 6171.
(5) Takano S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1989**, 359.
(6) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964,** *47*, 2425.

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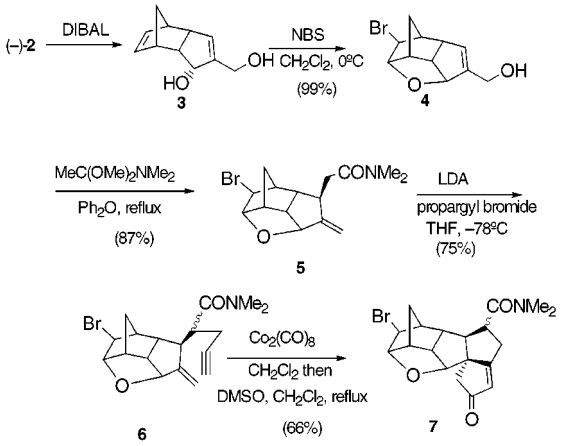
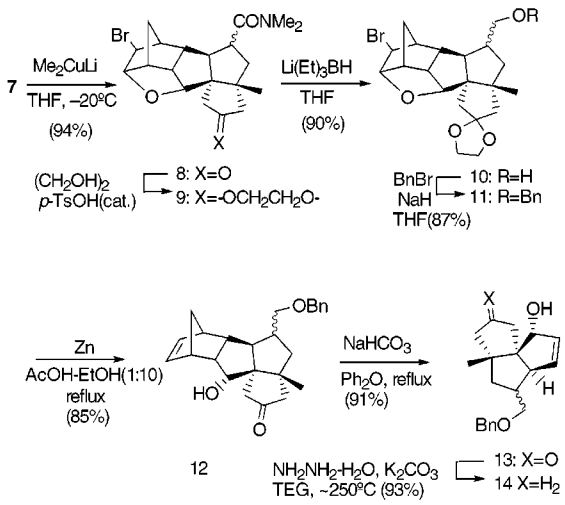
diastereoselectively the *exo*-acetamide **5**, $[\alpha]^{27}_D$ +57.0 (*c* 1.0, $CHCl_3$), as the single product. This was then alkylated with propargyl bromide to give the 1,5-enyne **6** as an inseparable 3:1 mixture. The formation of a mixture at this stage was ultimately of no consequence because this stereogenic center disappeared later in the synthesis. We, therefore, carried out the following conversion without separation of this epimeric mixture. Thus, the mixture, upon a Pauson−Khand reaction[7] in dichloromethane in the presence of dimethyl sulfoxide (DMSO),[8] afforded the expected polycyclic enone **7** in 66% yield as an inseparable mixture of two epimers (Scheme 2).

Scheme 2



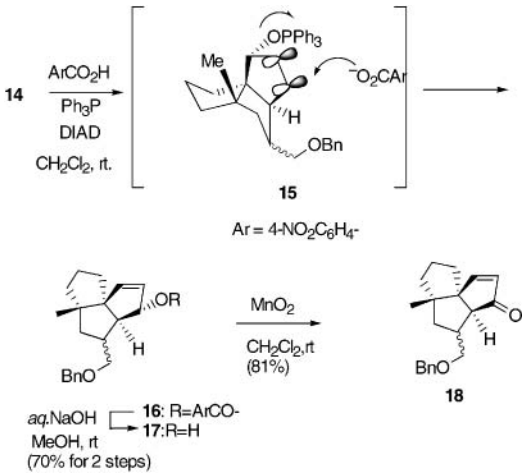
Having constructed the key enone intermediate **7** carrying the tricyclic core and two stereogenic centers required for the target molecule, one of the two requisite quaternary methyl functionalities was next introduced by reaction of **7** with a cuprate reagent to give the ketone **8** by diastereoselective 1,4-addition. The ketone **8** was transformed into the ketal **9** whose amide functionality was then transformed into the benzyl ether **11** via the primary alcohol **10** by sequential treatment with lithium triethylborohydride[9] and benzyl bromide. Exposure to zinc powder in refluxing ethanol containing acetic acid **11** liberated the olefin and the hydroxy functionalities by reductive cleavage of the bromo-ether linkage to afford the hydroxyketone **12** with concurrent deketalization under these conditions. At this point, thermolysis of **12** was carried out in refluxing diphenyl ether in the presence of sodium hydrogen carbonate[10] to leave the tricyclic ketoalcohol **13** in 91% yield with removal of the cyclopentane moiety by retro-Diels−Alder reaction. The ketone functionality of **13** was then reduced under Wolff−Kishner conditions[11] to give the allylic alcohol **14** (Scheme 3).

Scheme 3



To introduce the remaining two methyl functionalities required for the target molecule, **14** was first transformed into the enone **18** through a 1,3-oxygen transposition. After considerable experimentation, the Mitsunobu reaction[12] was found to be the most appropriate for this purpose. Thus, treatment of **14** with 4-nitrobenzoic acid[13] in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine furnished regio- and diastereoselectively the *exo*-allyl benzoate **16** as a single regioisomer, presumably by intervention of the phosphonium intermediate **15** which only allows SN2′ substitution owing to the steric congestion of the opposite face preventing SN2 substitution. The desired enone **18** was obtained from **16** via the allylic alcohol **17** on sequential alkaline methanolysis and oxidation (Scheme 4).

Scheme 4

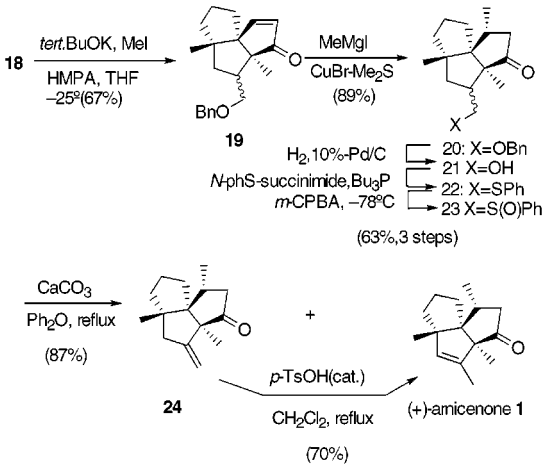


The quaternary methyl functionality was first introduced diastereoselectively by treating **18** with iodomethane and

(7) For a recent review, see: Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263.
(8) Keum, Y.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220.
(9) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.
(10) Kamikubo; T.; Ogasawara, K. *Chem. Commun.* **1995**, 1951.
(11) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301
(12) Mitsunobu, O. *Synthesis* **1981**, 1. Hughes, D. L. *Org. React.* **1992**, *42*, 335.
(13) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

potassium *tert*-butoxide in THF in the presence of hexamethylphosphoric triamide (HMPA) to give **19**. In the absence of HMPA, the reaction proceeded very slowly and in an incomplete manner. The tertiary methyl functionality was then introduced in a 1,4-addition reaction by treating **19** with a cuprate reagent to give the single ketone **20**, diastereoselectively. On sequential debenzylation, phenyl sulfide formation,[14] and oxidation, **20** furnished the sulfoxide **23** via the primary alcohol **21** and the phenyl sulfide **22** in satisfactory overall yield. Finally, **23** was refluxed with calcium carbonate in diphenyl ether to give a mixture (1:1.2) of the *exo*-methyleneketone **24** and (+)-arnicenone **1**, which was separated by silica gel column chromatography to give (+)-arnicenone **1**, as a colorless solid, $[\alpha]^{27}_{D}$ +592 (*c* 0.7, benzene) [natural[3]: mp 80−85 °C, $[\alpha]^{20}_{D}$ +614 (*c* 0.1, benzene)] and the *exo*-olefin isomer **24**, $[\alpha]^{27}_{D}$ −83.0 (*c* 0.4, benzene), as a colorless oil. The latter afforded the former on reflux in dichloromethane in the presence of *p*-toluenesulfonic acid. Spectroscopic data of (+)-arnicenone **1** thus obtained were identical with those reported for the natural product.[3] Thus, the absolute configuration was determined as 1*R*,3a*R*,5a*S*,8a*R* by correlation with the configuration of the starting chiral building block (−)-**2**. Since natural (+)-arnicenone **1** has been transformed into (−)-isocomene[3,15,16] **1** (=O = =H_2), the present synthesis constitutes its first enantiocontrolled synthesis in the formal sense. Moreover, the stereochemical determination of the isocomene-type angular triquinane sesquiterpenes based on the complex rearrangement pathway[4] has been proven unambiguously (Scheme 5).

Scheme 5



In conclusion, we have achieved the first enantiocontrolled synthesis of (+)-arnicenone on the basis of the inherent steric nature of the chiral building block used and have determined the absolute configuration of the natural product.

Acknowledgment. The authors thank the Ministry of Education, Science, Sports and Culture, Japan, for financial support.

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(14) Walker, K. A. M. *Tetrahedron Lett.* **1977**, 4475.

(15) Racemic arnicenone has been synthesized as an intermediate of Paquette's synthesis of racemic α-isocomene (±)-**1** (=O = =H_2), see: Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1835.

(16) Quite recently, the starting material used in the Paquette synthesis has been synthesized in a single enantiomeric form, see: Urabe, H.; Hideura, D.; Sato, F. *Org. Lett.* **2000**, *2*, 381.